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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,557	12/04/2001	Pasqualino Loi	LOI=1	8858

7590 02/01/2005  
Browdy and Neimark  
624 Ninth Street N W Suite 300  
Washington, DC 20001

EXAMINER
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CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 02/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/980,557

**Applicant(s)**

LOI ET AL.

**Examiner**

Deborah Crouch, Ph.D.

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 November 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 42-44, 47-55, 57, 59-64 and 66-69 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 42-44, 47-55, 57, 59-64 and 66-69 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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Applicant's arguments filed November 9, 2004 have been fully considered. The new rejection below necessitated this non-final office action. The amendment has been entered. Applicant's response is not addressed as each rejection below is new.

Claim 69 contains a misspelled word: "steep" should be "step." Applicant should review the specification for additional errors.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-44, 47-55, 57, 59-64, and 66-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of reconstructing a non-primate mammalian embryo comprising transferring into an enucleated metaphase II oocyte a G1 or G0 donor cell or donor cell nucleus of the same species as the oocyte where the chromatin within the nucleus had been subject to thermal denaturation prior to transfer to the oocyte, where the embryo is specifically a mouse embryo, the process of reconstructing an ungulate embryo selected from the group consisting of sheep and goat and a process for generating animal comprising culturing the reconstructed embryo to a blastocyst, transferring the blastocyst to a female of the same species, causing the blastocyst to develop to term and breeding the resulting animal, does not reasonably provide enablement for the process of reconstructing primate, rat, rabbit, guinea pig, fur species, pig, water buffalo or horse embryos where the chromatin had been denatured by any other process. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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With regard to genus nonhuman mammal, and species rat, rabbit, guinea pig, fur species, pig, water buffalo or horse, at the time of filing the art taught that the production of primate mammals and horses was unpredictable. Pennisi cites several scientists working in the area of mammalian cloning who point to a lack of general and reproducible success, thus, emphasizing the lack of predictability at the time of filing. Robert Wall of the USDA is quoted as stating that despite years of effort, "[w]e're in the same bind that we've always been in. A majority of [would be clones] do not make it to term." (Pennisi and Vogel (2000), page 1722, col. 1, parag. 2, lines 9-14). Pennisi and Vogel state that "even when an embryo does successfully implant in the womb, pregnancies often end in miscarriages" (Pennisi and Vogel (2000), page 1722, col. 1, parag. 3, lines 16-18). As the authors state, establishing pregnancies is only part of the problem and is not a guarantee of a cloned mammal being produced (Pennisi and Vogel (2000), page 1726, col. 2, lines 9-11). Tiger clones, a fur species, were lost well after pregnancy was established, as were domestic cats and rabbits. *Korean Now* (May 31, 2003) reports that a tiger became pregnant with a cloned tiger embryo made using a cow embryo, but that the tiger had a miscarriage. *The Wall Street Journal* (March 19, 2002) reports that an effort to clone a Siberian tiger but that cloning attempts have failed, although a tiger embryo was produced by nuclear transfer using a bovine oocyte. With particular regards to primates two cloned monkeys were produced, but there have been no subsequent successes in primate cloning (Pennisi and Vogel (2000), page 1726, col. 2, line 6 to col. 3, line 3). In this regard, is a post-filing report in 2002 that the cloning of monkeys, a primate, by nuclear transfer had been successful when embryonic cells were the nuclear donor, not when somatic cells were used as nuclear donor (Mitalipov, abstract). Fourteen somatic cell NT embryos were transferred to 3 recipients (Mitalipov, page 1371, col. 1, parag. 1, lines 5-7). Mitalipov states that nuclear reprogramming is a limiting parameter in monkey somatic cell cloning (page 1371,

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col. 1, parag. 2, lines 13-25). Mitalipov further states, clearly, that somatic cell cloning has not been accomplished in primates (Mitalipov, page 1367, col. 2, parag. 3, lines 1-3). With regard to the particularly claimed species "horse" (claim 63) at the time of filing, the production of horses by somatic cell nuclear transfer, as presently claimed was regarded as unpredictable. Cloned horses were not produced until 2003, four years after applicant's earliest priority date (Vanderwall, page 675, col. 1, lines 1-4). This is unlike cattle which have been cloned from a variety of adult cells (Vanderwall, page 675, col. 1-2, bridg. sent). Further, in reporting the birth of a cloned horse, Galli states that the success was aided by advances in assisted reproduction in the horse, including oocyte activation and zona-free manipulation (Galli, page 635, col. 2, parag. 1, lines 7-13). These techniques, nor others, are disclosed in the present specification. Fitchev states that reconstituted rat embryos were transferred to the uterus of surrogate mothers but none developed to term (Fitchev, page 1528, col. 1, parag. 1, lines 1-3). With regard to rabbits, Chesne states that success in rabbit nuclear transfer was achieved by taking into account species differences (page 366, col. 1, parag. 1, lines 10-13 and page 367, col. 2, parag. 1). As of applicant's effective filing date of 1999, only one piglet had been produced by nuclear transfer using an embryonic cell and none when an adult or somatic cell was the nucleus donor, although similar methodology was successful in cloning sheep, cattle, mice and goats (Polejaeva, abstract, lines 5-8 and 12-16). Polejaeva teaches a methodology for producing pigs by nuclear transfer, however, this method is significantly different from that used in cloning of sheep, cattle, mice and goats (page 87, figure 1). The specification provides no guidance for the production of pigs by nuclear transfer at the time of filing. Further, at applicant's effective filing date, 1999, the art did not teach the cloning of water buffalo or guinea pigs, and no guidance is provided by the specification for the cloning of these species of animals. Given the unpredictability established for rat, rabbit, fur species, pig and horse, there is a

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reasonable expectation that the cloning of guinea pigs and water buffalo would also be regarded as unpredictable. At the time of filing, it pointed out that *Bos taurus* genus-species cattle had been cloned. Water buffalo is not of the *Bos* genus but is of the *Bubalus* genus. Thus, it is unpredictable that methods for cloning *Bos* by nuclear transfer would be enabling for the cloning of *Bubalus* by nuclear transfer.

Further, as stated by the previously, in the production of sheep goat chimeras, there were biases towards chimeras whose genotype and phenotype was most like that of the recipient, and that the successful production of chimeras resided in the neutralization of incompatibility between the chimeric embryo (Fehilly et al (1985), page 221, parag. 1). This is also an unpredictable feature of the claimed invention as an embryo of one species implanted into a surrogate mother of another species is unlikely to develop given the teaching of Fehilly. The specification does not provide guidance on producing cross-species embryo or animals, nor how to overcome the unpredictable nature of cross-species cloning. Guidance is not provided in the present specification to overcome this cross-species barrier. While nuclear transfer using sheep cells and oocytes, bovine cells and oocytes, or goat cells and oocytes might result in live births in certain methodologies, it was unpredictable at the time of filing that sheep x bovine, sheep x goat nuclear transfer procedures, and the like combinations would lead to live births. It is evident from Fehilly that the surrogate mother needs to be of the same species as the oocyte and donor nucleus. "Suitable implant animal" is not enabled for its breadth.

In summary, for allowance and in the absence of persuasive arguments or evidence, the claims need to be limited to nonprimate mammals, in claim 61, the limitation needs to be to mouse only, in claim 63, the limitation needs to be to cattle, sheep and goat, where "cattle" includes only *Bos* genus animals and in claim 64 that the blastocyst is transferred to a female of the same species as the donor cell and oocyte.

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In addition, claim 67 is not enabled because at the time of filing, whole embryo genetic modification was not enabled. The methodology was not available to modify a multicellular embryo, especially once implanted into the surrogate mother.

Thus, the art at the time of filing clearly indicates that full breadth of the claimed invention was not enabled. Thus, the skilled artisan would have needed to conduct an undue amount of experimentation without a predictable degree of success to implement the claimed invention for its entire breadth.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 64 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 64 is confusing. In step "c" it is not clear if "animal embryo" refers to the animal embryo of step "a" or the blastocyst of step "b." If it meant that the blastocyst develops in step "c," then animal embryo lack antecedent basis.

Claim 67 is confusing as any genetic modification would need to be done prior to term in an embryo. Embryos are nonexistent at term.

The claims are free of the prior art. At the time of the present invention, the prior art did not teach or suggest a process for reconstituting an animal embryo or a process for generating an animal as claimed where the donor cell or donor cell nucleus is denatured prior to insertion into the recipient oocyte.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Deborah Crouch, Ph.D.  
Primary Examiner  
Art Unit 1632

January 31, 2005